



**Karolinska
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Institutionen för Mikrobiologi, Tumör- och Cellbiologi

Regulation of B cell responses to modified self

AKADEMISK AVHANDLING

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ABSTRACT

The immune system needs to be efficient to protect organisms from invading pathogens. Lymphoid organs such as the spleen and lymph nodes are needed to initiate the response. The spleen is important for systemic immunity and filters the blood for blood-borne pathogens through its marginal zone, where marginal zone macrophages (MZM) and marginal zone B cells (MZB) reside. Part of the immune surveillance is carried out by scavenger receptors expressed by these cell types, as well as by natural antibodies produced by B cells that help to clear and engulf pathogens. The same scavenger receptors also recognize self and it is therefore crucial that the cells of the immune system are properly regulated to give a pro-inflammatory response when responding to non-self while inducing anti-inflammatory responses when recognizing self. When this balance is broken, the immune system turns against its own body, causing so-called autoimmune diseases.

The aim of the work presented in my thesis was to investigate how B cells are regulated by components of innate immunity in the response to modified self, through the study of animal models for autoimmunity and atherosclerosis. In **paper I**, we investigated how the inflammatory cytokine IL-18 induces a potent antibody response. We found that IL-18 drives a MZB expansion leading to primarily extrafollicular foci responses and that the ensuing self-response is regulated by innate natural killer T cells (NKT). In **paper II**, we investigated how NKT cells regulate autoreactive B cells in a model where syngeneic apoptotic cells were injected repeatedly to break tolerance to self and induce an autoantibody response. We show that NKT cells make up an important CD1d-dependent check-point for autoreactive B cells prior to germinal center entry and that transfer of NKT cells lowers the load of autoantibodies. In **paper III**, we studied the role of scavenger receptor CD36 expressed on MZBs in this context. We found that down-regulation of CD36 coincides with germinal center formation, that B cells lacking CD36 are more easily activated towards apoptotic cells and that CD36 exert its inhibitory effect on autoreactive B cells by associating with the tyrosine kinase Lyn and FcγRIIb. In **paper IV**, we investigated the role of the spleen, the recognition of modified self in atherosclerosis and how this is regulating an inducible protective B cell response. Transfer of spleen B cells from old atherosclerosis-prone ApoE^{-/-} mice to young ApoE^{-/-} mice has previously been shown to confer protection against plaque development. We found lipid-driven germinal center and plasma cell foci populations in the spleens of old ApoE^{-/-} mice. Administration of apoptotic cells, carrying the same oxidation specific epitopes as modified low-density lipoprotein (LDL), led to the same activated phenotype, protected against atherosclerosis, and led to a B cell-dependent cholesterol decrease through the production of anti-oxLDL IgM.

In summary, the work presented here describes how autoreactive B cells are regulated extrinsically by components of the innate immune system such as IL-18, which drives autoantibody production and by NKT cells that inhibit them. B cells are also regulated intrinsically by inhibitory receptors on their surface and we found a novel co-receptor involved in response to self-antigen. However, autoreactive B cells can also drive protective responses in atherosclerosis-prone mice. By studying how they are regulated, we can learn how to inhibit harmful while promoting protective responses and hopefully apply this knowledge to therapeutic approaches in the future.